

Clinical Medicine

Differentiating Pyogenic Arthritis From Spontaneous Hemarthrosis in Patients With Hemophilia

RICHARD T. ELLISON III, MD, and L. BARTH RELLER, MD, Denver

Pyogenic arthritis in patients with hemophilia is predominantly monoarticular, usually involving the knee, is associated with hemophilic arthropathy and other predisposing factors for infection, is mainly due to Staphylococcus aureus and carries serious morbidity. In patients with hemophilia, it is associated significantly with fever, an increased leukocyte count, knee joint involvement and possible predisposing factors for infection. Such patients presenting with unexplained fever of more than 1°C (1.8°F) and acute symptoms of joint inflammation should have an arthrocentesis.

(Ellison RT III, Reller LB: Differentiating pyogenic arthritis from spontaneous hemarthrosis in patients with hemophilia. West J Med 1986 Jan; 144:42-45)

Trauma, chronic arthropathy due to rheumatoid arthritis or osteoarthritis and intravenous drug abuse have all been considered risk factors for the development of pyogenic arthritis.¹⁻³ Although hemophilia is associated with frequent hemarthroses, chronic arthropathy and the frequent use of intravenous transfusions, only 11 patients with hemophilia have been reported to have pyogenic arthritis.⁴⁻¹⁵ Treatment of two patients with hemophilia who had joint infections at our hospital in a 19-month period suggested that pyogenic arthritis might be an underrecognized complication of hemophilia. Our study was undertaken to describe the frequency of pyogenic arthritis in patients with hemophilia, to characterize the clinical features of these infections and to compare the presentation of pyogenic arthritis with that of spontaneous hemarthrosis in an attempt to define distinguishing characteristics.

Patients and Methods

The medical records of the University of Colorado Hospital (UCH) were reviewed for all patients discharged with concurrent diagnoses of pyogenic arthritis and hemophilia, rheumatoid arthritis or osteoarthritis. The period from 1952 through 1982 was reviewed for pyogenic arthritis and hemophilia and from 1977 through 1982 for the other conditions. Reviews for pyogenic arthritis and hemophilia were similarly carried out for the period 1972 to 1982 at the Rose Medical Center, St Luke's Hospital and Presbyterian Medical Center

in Denver. A questionnaire was mailed to all patients registered at the Mountain States Regional Hemophilia Center (MSRHC).

Records of all patients with hemophilia admitted to UCH during the period July 1980 to June 1982 were reviewed. Charts from all hospital admissions and emergency room visits that showed both a diagnosis of hemarthrosis and a recorded body temperature were evaluated. Because a subset of patients with hemophilia received almost all of their care at UCH, in an attempt to limit skewing of data by this subset, only the first ten visits meeting the selection criteria were reviewed for each patient.

A computer search of medical literature from 1966 through 1984 was made for infectious arthritis and hemophilia. Statistical analysis was done with a one-way analysis of variance and the χ^2 test.

Results

Frequency of Infectious Arthritis and Hemophilia Among Patients Admitted to Hospital

Between 1952 and June 1982, 495 patients with hemophilia were admitted to the University of Colorado Health Sciences Center among about 400,000 total admissions to this institution. Three of these patients had pyogenic arthritis during this period and a fourth patient with hemophilia and pyogenic arthritis was admitted in December 1982. In the period between July 1977 and June 1982, there were five

From the Infectious Disease Section, Veterans Administration Medical Center, and the Division of Infectious Diseases, Department of Medicine, University of Colorado School of Medicine, Denver.

Submitted, revised, April 8, 1985.

This project was supported by the Veterans Administration Research Service.

Reprint requests to Richard T. Ellison III, MD, Infectious Disease Section (111L), VA Medical Center, 1055 Clermont St, Denver, CO 80220.

ABBREVIATIONS USED IN TEXT

MSRHC = Mountain States Regional Hemophilia Center
UCH = University of Colorado Hospital

episodes of pyogenic arthritis among 455 patients admitted with rheumatoid arthritis and two episodes among 515 patients with osteoarthritis.

A review of the medical records between July 1977 and June 1982 at three community hospitals found 14 patients with hemophilia admitted among about 205,000 admissions; one additional patient with hemophilia and pyogenic arthritis was identified.

Frequency of Pyogenic Arthritis in Patients With Hemophilia

Through the MSRHC, 180 patients with hemophilia were identified and mailed questionnaires. There were 95 (53%) respondents, of whom 77 (81%) had a history of hemarthroses. Although many patients responded with only estimates, those patients having had a hemarthrosis reported more than 11,000 subjective hemarthroses, with a mean of 148 per patient (range 1 to 500). The mean age of the population was 19.7 ± 1.5 (standard error of the mean) years (range 1.5 to 62 years) and the total years of life was 1,752. Two patients in this population each had a single episode of pyogenic arthritis in a knee. These two patients and two additional patients who did not respond to the questionnaire were known to have had pyogenic arthritis by the medical record review. Of the patients with hemophilia, 20 reported having had a total of 38 joint operations, none of which was associated with joint infection.

Comparison of Spontaneous Hemarthrosis and Pyogenic Arthritis in Hemophilia

A review of the records of 38 patients with hemophilia seen at UCH disclosed 32 outpatient and 35 inpatient encounters in 15 patients where the inclusion criteria of a chart diagnosis of hemarthrosis and a recorded body temperature were met. Many additional outpatient encounters occurred, but in these instances a temperature was not recorded. These hemarthrosis episodes were compared with the details of eight cases of pyogenic arthritis in patients with hemophilia

reported in the literature and five Denver cases (one case of a patient admitted to UCH has been reported previously⁹ and minimal clinical details are available for the other cases in the literature).⁴⁻¹⁵ The general characteristics of each group are noted in Table 1.

The patients with spontaneous hemarthrosis were younger than those with pyogenic arthritis ($P < .01$) but were comparable in severity of hemophilia and prevalence of hemophilic arthropathy. The distributions of joint involvement of hemarthrosis in the inpatient and outpatient encounters were similar and were also comparable to those of reported series.¹⁶ They differed significantly ($P < .05$), however, from the joint distribution of pyogenic arthritis, where the knee alone was involved with infection in ten cases and the hip alone in an additional case. Two of the patients with pyogenic arthritis, one with a history of intravenous drug use, had simultaneous involvement of multiple joints without evidence of endocarditis. Aside from this patient using intravenous drugs, four other patients with pyogenic arthritis each had a predisposing factor for joint infection, including one each with a previous joint aspiration and hemodialysis and two with prior total-knee arthroplasties. None of the eight remaining infected patients had a readily identifiable explanation for the development of pyogenic arthritis other than hemophilic arthropathy. In comparison, a possible predisposing factor for infection was identified in only two hemarthrosis encounters: a surgical procedure in the involved joint three months before presentation in one patient and concurrent gonococcal urethritis in another.

The duration of symptoms before evaluation in the patients with hemarthrosis was significantly shorter than the time to presentation in the nine patients with pyogenic arthritis where information was available ($P < .0001$). A complete description of the involved joint typically was not recorded in the hemarthrosis encounters, but all patients with hemarthrosis had joint pain, 88% had joint swelling, 70% had joint tenderness, 39% had joint warmth and 9% had joint discoloration recorded. Where information was available, all patients with pyogenic arthritis had pain, tenderness and swelling of the involved joint.

The initial temperatures were comparable in the inpatient and outpatient hemarthrosis encounters ($36.8 \pm 0.1^\circ\text{C}$). These temperatures were significantly lower than those ini-

TABLE 1.—Pyogenic Arthritis and Spontaneous Hemarthrosis in Hemophilia

TABLE 1.—Pyogenic Arthritis and Spontaneous Hemarthrosis in Hemophilia			
General Characteristics	Pyogenic Arthritis N = 13	Spontaneous Hemarthrosis N = 67	P
	mean ± standard error of the mean		
Age, years	32.5 ± 4.1	22.7 ± 1.8	< .01
Hemophilic arthropathy	11/11	8/14	> .05
Joint distribution			< .05
Shoulder	3	5	
Elbow	2	15	
Wrist	1	5	
Hip	1	4	
Knee	12	23	
Ankle	3	29	
Predisposing factors for infection	5	2	< .001
Duration of symptoms before presentation, days	3.8 ± 0.5	1.4 ± 0.2	< .0001
Body temperature, °C	38.8 ± 0.4	36.8 ± 0.1	< .0001
Peripheral leukocyte count, per μl	12,532.0 ± 1,825	7,900.0 ± 580	< .01

tially recorded in patients with pyogenic arthritis where a temperature higher than 38°C (100.4°F) was noted within 12 hours of presentation in 9 of 11 patients for whom the temperature was recorded ($P < .000001$).^{*} The mean duration of inpatient stay for patients admitted to hospital for hemarthrosis was 4.8 ± 0.5 days, and the peak in-hospital temperatures were also lower than the initial temperatures in patients with pyogenic arthritis ($P < .0001$). Only one patient with a hemarthrosis had an initial temperature higher than 38.0°C: a 6-year-old boy with both a knee hemarthrosis and a large soft tissue hematoma of the arm. He had an initial temperature of 38.8°C (101.8°F) and a peak in-hospital temperature of 39.4°C (102.9°F). During an eight-day hospital stay, his temperature was ascribed to his soft tissue hematoma, no other cause was identified and his condition improved with only supportive care. Three additional inpatients had peak in-hospital temperatures of greater than 38.0°C: a 2-year-old boy who was diagnosed as having Henoch-Schönlein purpura; a 20-year-old man in whom nausea, vomiting, diarrhea and fever developed on the third hospital day, and a 16-year-old boy with both a soft tissue hematoma and an ankle hemarthrosis in whom an unexplained self-limited fever developed on the second and third hospital days without any additional symptoms.

The peripheral leukocyte count was significantly lower ($P < .001$) in the 32 hemarthrosis encounters in which it was measured than it was in the episodes of pyogenic arthritis (Table 1). Only three patients with hemarthroses had a leukocyte count higher than 10,000 per μl , and only one had a leukocyte count higher than 12,500 per μl . This was the patient with the large soft tissue hematoma who had a leukocyte count of 23,300 per μl . Synovial fluid leukocyte counts were measured in six cases of pyogenic arthritis; the mean count was $220,000 \pm 60,200$ per μl .

Additional Features of Pyogenic Arthritis in Hemophilia

In 9 of the 13 episodes, *Staphylococcus aureus* was the pathogen, and in a tenth Gram-positive cocci were seen on Gram's stain, although cultures of specimens taken while the patient was on antibiotic therapy showed no growth. One patient had infection with *Streptococcus pneumoniae* and the two cases that occurred after total-knee arthroplasties were due to Gram-negative bacilli (*Enterobacter* species in one patient and both *Pseudomonas aeruginosa* and *Escherichia coli* in the second).

The mean duration of symptoms before the diagnosis of pyogenic arthritis was 5.4 ± 0.8 days with a range of 2 to 10 days. Appropriate antibiotic therapy was used in the 12 cases for whom information is available. Eight patients were treated with surgical drainage and three patients with multiple needle aspirations. While all the patients survived, significant complications were noted in eight patients, including five of the eight who had open drainage. Six patients had fever for more than ten days and three patients had superinfection (*Pseudomonas* species, *E coli*, group A *Streptococcus pyogenes* and *Enterobacter cloacae*) after open drainage. Two patients had amputations and the two patients with the infected total-knee arthroplasties had the implants removed.

^{*}A temperature of 37.0°C (98.6°F) was used for this analysis for the one patient with pyogenic arthritis in the literature who was "afebrile" at initial evaluation.¹⁵

Discussion

Although only 11 patients with hemophilia have previously been reported to have pyogenic arthritis, our finding of 5 patients (including 1 of these 11 reported cases) in one city suggests that this is an important complication of hemophilia. Data from a questionnaire sent to all persons with hemophilia followed through the MSRHC suggest a frequency of two episodes of pyogenic arthritis per 1,752 years of life.

With the high frequency of hemarthroses seen in patients with hemophilia, it seems unlikely that this alone contributes to the risk of infection. This is supported by data in animals showing that intraarticular injection of autologous blood does not increase susceptibility to infection.¹⁷ Analysis of our cases and those previously reported indicates that pyogenic arthritis tends to occur in an older population of persons with hemophilia in association with hemophilic arthropathy, thus suggesting that chronic arthropathy is a contributing factor. If this is the major pathogenic factor, then it is possible that its incidence will increase in the future as the use of factor VIII preparations allows longer life spans in patients with severe hemophilia.¹⁸

Pyogenic arthritis in our patients was comparable to other series of nongonococcal septic arthritis in that the illness was predominantly monoarticular, the knee was the most commonly affected joint and *S aureus* was the most frequent pathogen. Although a predisposing factor for infection was present in some of our patients, in more than half the only apparent risk factor was hemophilic arthropathy. There were not sufficient data to analyze the results of therapy in the patients with hemophilia, but there was a high frequency of complications. Of particular concern is the finding of Gram-negative rod superinfection following open drainage in three patients, a complication that has not been noted in any patient in other recent series of cases of septic arthritis.^{1,2,10,19-24}

The ability to rapidly diagnose pyogenic arthritis in patients with hemophilia is hindered by the frequent occurrence of spontaneous hemarthrosis, an illness with comparably rapid onset, joint distribution and local physical findings. In comparing pyogenic arthritis and hemarthrosis encounters, the findings of our study suggest that there is a subset of patients with hemophilia presenting with the acute development of articular pain and tenderness who may have a higher frequency of joint infection, including those persons with an otherwise unexplained fever of greater than 1°C (38.0°C), an elevated peripheral leukocyte count of more than 10,000 per μl , possible predisposing factors for infection, knee-joint involvement and hemophilic arthropathy. Additionally, the diagnosis of pyogenic arthritis should be considered in patients who have prolonged joint symptoms that do not respond to the standard therapy for hemophilic hemarthrosis. These clinical characteristics are not of equal weight in distinguishing pyogenic arthritis from hemarthrosis. A recorded temperature of higher than 38.0°C was atypical of cases of uncomplicated hemarthroses, either at presentation or during their evolution, whereas it was present early in almost all patients with pyogenic arthritis not receiving antibiotic therapy.

Arthrocentesis has been considered an unnecessary procedure in the management of hemophilic hemarthrosis, as the data obtained do not modify subsequent therapy and there is a risk for increased bleeding or infection.²⁵ Yet, pyogenic ar-

thrititis in a patient with hemophilia carries a high morbidity that might be lessened by an earlier diagnosis.¹⁹ We feel that in any such patient presenting with an acutely inflamed joint and an otherwise unexplained fever of more than 1°C (1.8°F), there should be strong consideration given to an early arthrocentesis, particularly if there has been poor response to standard hemarthrosis therapy or any other suggestive characteristics of infection. In the absence of fever, however, given the low ratio of infectious events to hemarthroses, the other characteristics of pyogenic arthritis are not adequately distinctive for infection, either alone or in combination, to justify doing an arthrocentesis. In such circumstances, they should serve as indicators for close observation and follow-up. The clinical utility of these suggestions ideally should be subjected to a prospective evaluation.

Addendum

Another patient with severe hemophilia A and pyogenic arthritis has been admitted to UCH. The patient, a 34-year-old man, presented with three days of fever to 39.5°C (103.1°F), chills and inflammation of the left elbow that had not responded to an intravenous infusion of factor VIII. He has hemophilic arthropathy of this joint and had had a Broviac catheter in place for five months for venous access. Cultures of specimens of blood and synovial fluid grew *S aureus*. The patient has had open drainage of the joint and is currently receiving intravenous antibiotic therapy.

REFERENCES

1. Goldenberg DL, Cohen AS: Acute infectious arthritis: A review of patients with nongonococcal joint infections (with emphasis on therapy and prognosis). *Am J Med* 1976; 60:369-377
2. Sharp JT, Lidsky MD, Duffy J, et al: Infectious arthritis. *Arch Intern Med* 1979; 139:1125-1130
3. Ward JR, Atcheson SG: Infectious arthritis. *Med Clin North Am* 1977; 61:313-329
4. Staas WE Jr, Ditunno JF, Gartland JJ, et al: Lower extremity amputation in hemophilia: Case report and review of surgical principles. *J Bone Joint Surg (Am)* 1972; 54:1514-1522
5. Miller EH, Flessa HC, Glueck HI: The management of deep soft tissue bleeding and hemarthrosis in hemophilia. *Clin Orthop* 1972; 82:92-107
6. Houghton GR: Septic arthritis of the hip in a hemophiliac: Report of a case. *Clin Orthop* 1977; 129:223-224
7. Rosner SM, Bhogal RS: Infectious arthritis in a hemophiliac. *J Rheumatol* 1981; 8:519-521
8. Moseley P, Gold RM, Field S, et al: Hemophilia, maintenance hemodialysis, and septic arthritis. *Arch Intern Med* 1981; 141:138-139
9. Wilkins RM, Wiedel JD: Septic arthritis of the knee in a hemophiliac: A case report. *J Bone Joint Surg (Am)* 1983; 65:267-268
10. Myers AR, Miller LM, Pinals RS: Pyarthrosis complicating rheumatoid arthritis. *Lancet* 1969; 2:714-716
11. Goldberg VM, Heiple KG, Ratnoff OD, et al: Total knee arthroplasty in classic hemophilia. *J Bone Joint Surg (Am)* 1981; 63:695-701
12. McCollough NC III, Enis JE, Lovitt J, et al: Synovectomy or total replacement of the knee in hemophilia. *J Bone Joint Surg (Am)* 1979; 61:69-75
13. Goldsmith JC, Silberstein PT, Fromm RE Jr, et al: Hemophilic arthropathy complicated by polyarticular septic arthritis. *Acta Haematol* 1984; 71:121-123
14. Cobb WB: Septic polyarthritis in a hemophiliac. *J Rheumatol* 1984; 11:87-89
15. Hofmann A, Wyatt R, Bybee B: Septic arthritis of the knee in a 12-year-old hemophiliac. *J Pediatr Orthop* 1984; 4:498-499
16. Stuart J, Davies SH, Cumming RA, et al: Haemorrhagic episodes in haemophilia: A 5-year prospective study. *Br Med J* 1966; 2:1624-1626
17. Schurman DJ, Johnson BL Jr, Amstutz HC: Knee joint infections with *Staphylococcus aureus* and *Micrococcus* species: Influence of antibiotics, metal debris, bacteremia, blood, and steroids in a rabbit model. *J Bone Joint Surg (Am)* 1975; 57:40-49
18. Ikkala E, Helske T, Myllylä G, et al: Changes in the life expectancy of patients with severe haemophilia A in Finland in 1930-1979. *Br J Haematol* 1982; 52:7-12
19. Ho G Jr, Su EY: Therapy for septic arthritis. *JAMA* 1982; 247:797-800
20. Goldenberg DL, Brandt KD, Cohen AS, et al: Treatment of septic arthritis: Comparison of needle aspiration and surgery as initial modes of joint drainage. *Arthritis Rheum* 1975; 18:83-90
21. Bayer AS, Chow AW, Louie JS, et al: Gram-negative bacillary septic arthritis: Clinical, radiographic, therapeutic, and prognostic features. *Semin Arthritis Rheum* 1977; 7:123-132
22. Manshady BM, Thompson GR, Weiss JJ: Septic arthritis in a general hospital 1966-1977. *J Rheumatol* 1980; 7:523-530
23. Rosenthal J, Bole GG, Robinson WD: Acute nongonococcal infectious arthritis: Evaluation of risk factors, therapy, and outcome. *Arthritis Rheum* 1980; 23:889-897
24. Bynum DK Jr, Nunley JA, Goldner JL, et al: Pyogenic arthritis: Emphasis on the need for surgical drainage of the infected joint. *South Med J* 1982; 75:1232-1235
25. Kisker CT, Perlman AW, Benton C: Arthritis in hemophilia. *Semin Arthritis Rheum* 1971; 1:220-235